

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re U.S. Patent Application of: )  
Jeffrey Owen Phillips )  
Serial No.: 09/901,942 ) Examiner: J. Fan  
Filed: July 9, 2001 ) Group Art Unit: 1625  
For: Novel Substituted Benzimidazole )  
Dosage Forms and Method of Using )  
Same )

CERTIFICATE OF MAILING BY "EXPRESS  
MAIL", mailing label number EL744237375US

Date of Deposit: July 1, 2002  
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under 37 CFR 1.10 on the date indicated above and  
is addressed to Assistant Commissioner of Patents,  
Washington, DC 20231

Timothy M. Hubalik  
(typed or printed name of person mailing paper or  
fee)  
(signature of person mailing paper or fee)

**TRANSMITTAL LETTER**

Assistant Commissioner of Patents  
Washington, D. C. 20231

Dear Sir:

Transmitted herewith for the above-captioned patent application are:

1. Amendment and Response to February 1, 2002 Office Action;
2. Request for one (1) month extension of time;
3. Terminal Disclaimer Under 37 CFR 1.321 to obviate a provisional double patenting rejection over a copending application;
4. Check in the amount of \$182, which includes: 1) \$55 submission fee under 37 CFR 1.20(d) for the Terminal Disclaimer, 2) \$55 for request for one-month extension of time, and 3) \$72 for additional claims;
5. Associate Power of Attorney;
6. English translation of the Japanese Patent Application No. 05194224;
7. English translation of the Japanese Patent Application No. 05194225;

8. Fee Transmittal Form; and
9. Post card, to acknowledge receipt of same.

The Commissioner is hereby authorized to charge any additional filing fees required under Rule 1.17 concerning this transaction, or to credit any overpayment to Deposit Account 13-0019.

Respectfully submitted,

By: 

Thomas R. Stiebel, Jr.  
Reg. No. 48,682

MAYER, BROWN, ROWE & MAW  
P.O. BOX 2828  
CHICAGO, ILLINOIS 60690-2828  
(312) 701-8775

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# FEE TRANSMITTAL for FY 2002

Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$) \$182.00

## Complete if Known

Application Number 09/901,942  
Filing Date July 9, 2001  
First Named Inventor Jeffrey O. Phillips  
Examiner Name J. Fan  
Group Art Unit 1625  
Attorney Docket No. 01723353

## METHOD OF PAYMENT (check all that apply)

☒ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number 13-0019  
Deposit Account Name Mayer, Brown, Rowe & Maw

The Commissioner is authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) during the pendency of this application

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

## FEE CALCULATION

### 1. BASIC FILING FEE

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	

SUBTOTAL (1) (\$)

### 2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

Extra Claims Fee from below Fee Paid  
Total Claims -20\*\* = 8 X 9 = \$72.00  
Independent Claims -3\*\* = 0 X 0 =  
Multiple Dependent = \$72.00

Large Entity		Small Entity		Fee Description
Fee Code	Fee (\$)	Fee Code	Fee (\$)	
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$) \$72.00

\*\*or number previously paid, if greater; For Reissues, see above

## FEE CALCULATION (continued)

### 3. ADDITIONAL FEES

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for ex parte reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	\$55.00
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,280	241	640	Petition to revive - unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR 1.17(q)	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR § 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	
Other fee (specify) Terminal Disclaimer					\$55.00
*Reduced by Basic Filing Fee Paid				SUBTOTAL (3) (\$)	\$110.00

## SUBMITTED BY

Name (Print/Type) Thomas R. Stiebel, Jr. Registration No. 48,682 Telephone 312-701-8775  
Signature [Signature] Date July 1, 2002

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

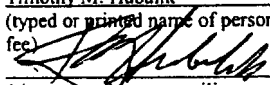
PATENT  
Docket No. 01723353

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re U.S. Patent Application of: )  
Jeffrey Owen Phillips )  
Serial No.: 09/901,942 ) Examiner: J. Fan  
Filed: July 9, 2001 ) Group Art Unit: 1625  
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Dosage Forms and Method of Using )  
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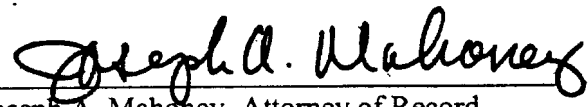
Assistant Commissioner for Patents  
Washington, DC 20231

Dear Sir:

**ASSOCIATE POWER OF ATTORNEY (37 C.F.R. section 1.34)**

Please recognize as Associate Practitioner in this case:

Thomas R. Stiebel, Jr., Reg. No. 48,682  
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By:   
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Reg. No. 38,956

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(312) 701-8979  
(312) 706-8530 fax  
Dated: July 1, 2002

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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Washington, DC 20231

Timothy M. Hubalik  
(typed or printed name of person mailing paper or  
fee)

\_\_\_\_\_  
(signature of person mailing paper or fee)

**TERMINAL DISCLAIMER UNDER 37 § CFR 1.321**

Assistant Commissioner of Patents  
Washington, D. C. 20231

Dear Sir:

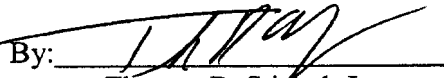
The assignee owner, Curators of the University of Missouri, a nonprofit organization, of a 100 percent interest in the instant (above-identified) Application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§ 154 to 156 and 173 as shortened by any terminal disclaimer filed prior to the grant of any patent granted on copending Application No. 09/481,207, filed on January 11, 2000, in which owner also has a 100 percent interest. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the second application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §§ 154 to 156 and 173 of any patent granted on the second application, as shortened by any terminal disclaimer filed prior to the patent grant, in the event that any such granted patent: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR § 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

The undersigned is an attorney of record, and the Terminal disclaimer fee under 37 CFR § 1.20(d) is included herewith.

Respectfully submitted,

Dated: July 1, 2002

By:   
Thomas R. Stiebel, Jr.  
Reg. No. 48,682

MAYER, BROWN, ROWE & MAW  
P.O. Box 2828  
Chicago, Illinois 60690-2828  
(312) 701-8775

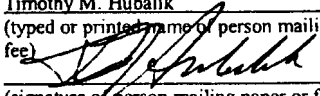
PATENT  
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Washington, DC 20231

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**REQUEST FOR EXTENSION OF TIME**

Assistant Commissioner for Patents  
Washington, D.C. 20231

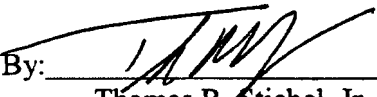
Dear Sir:

Applicant hereby petitions the Commissioner of Patents and Trademarks pursuant to Rule  
1.136 to extend the time for response to the office action dated February 1, 2002 for one (1)  
month from May 1, 2002. Enclosed is a check for \$55.00 to cover the cost of the extension.

The Commissioner is hereby authorized to charge any additional fees required, or credit  
any overpayment to Deposit Account No. 13-0019. A duplicate copy of this sheet is attached.

Respectfully submitted,

Dated: July 1, 2002

By:   
Thomas R. Stiebel, Jr.  
Reg. No. 48,682

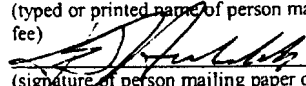
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Timothy M. Hubalik  
(typed or printed name of person mailing paper or  
fee)  
  
(signature of person mailing paper or fee)

**AMENDMENT AND RESPONSE TO FEBRUARY 1, 2002 OFFICE ACTION**

Assistant Commissioner of Patents  
Washington, D. C. 20231

Dear Sir:

This Amendment is submitted in response to the Office Action mailed February 1, 2002.

Submitted simultaneously herewith is a request for a one-month request for extension of time and the fee in the amount of \$55. With this one-month extension of time, this response is timely filed if filed on or before July 1, 2002 in accordance with 37 CFR § 1.10. If there are any additional fees due in connection with the filing of this response, please charge these additional fees (or credit any overpayment) associated with this communication to our Deposit Account No. 13-0019. Reconsideration and withdrawal of the outstanding rejections are respectfully requested. Applicant respectfully requests entry of the following Amendment. Applicant believes that entry of the following Amendment and the foregoing Remarks will place the claims in condition for Allowance.



## IN THE CLAIMS

### ***I. Cancellation of Claims***

To expedite prosecution, please cancel claims 2-5, and 7-20, without prejudice. By cancellation of these claims it is not to be construed as dedicating any such subject matter to the public, and Applicants reserve all rights to pursue any such subject matter in this or a related patent application.

### ***II. Substitution of Claims***

Please substitute the below pending claims with the corresponding amended claims, as shown below:

1. (Amended) A solid oral pharmaceutical dosage form that is not enteric-coated or delayed-release, comprising: active ingredients consisting essentially of:

(a) a non-enteric coated proton pump inhibitor (PPI) selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, free base, or salt thereof, in an amount of approximately 5 mg to approximately 300 mg;

(b) a Primary Essential Buffer; and

(c) an optional Secondary Essential Buffer;

wherein the total amount of the Primary Essential Buffer and the optional Secondary Essential Buffer is in an amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor; and

the composition is dissolvable by gastric fluid upon oral administration to a subject and upon dissolution releases the proton pump inhibitor, the Primary Essential Buffer, and the Secondary Essential Buffer into the gastric fluid elevating pH of the gastric fluid to at least 3.7

from time the proton pump inhibitor comes in contact with the gastric fluid throughout dwell time; and

the dosage form is selected from the group consisting of suspension tablet, chewable tablet, two-part tablet, effervescent powder, and effervescent tablet.

6. (Amended) The dosage form as recited in Claim 1, wherein the dwell time is equal to or less than about 30 minutes.

### ***III. Addition of New Claims***

Please add the following claims, as shown below:

21. The composition of claim 1, wherein the proton pump inhibitor is in an amount from approximately 10 mg to approximately 100 mg.
22. The composition of claim 1, wherein the proton pump inhibitor is omeprazole.
23. The composition of claim 1, wherein the proton pump inhibitor is lansoprazole.
24. The composition of claim 1, wherein the proton pump inhibitor is pantoprazole.
25. The composition of claim 1, wherein the proton pump inhibitor is rabeprazole.
26. The composition of claim 1, wherein the proton pump inhibitor is esomeprazole.
27. The composition of claim 1, wherein the proton pump inhibitor is pariprazole.
28. The composition of claim 1, wherein the proton pump inhibitor is leminoprazole.
29. The composition of claim 1, wherein the Primary Essential Buffer is selected from the group consisting of sodium bicarbonate, sodium sesquicarbonate, dibasic sodium phosphate, sodium tripolyphosphate, tetrasodium pyrophosphate, sodium citrate, calcium citrate, calcium carbonate, magnesium oxide, sodium gluconate, sodium lactate, sodium acetate, dipotassium phosphate, tetrapotassium pyrophosphate, potassium bicarbonate, calcium lactate,

calcium glycerophosphate, calcium gluconate, magnesium lactate, magnesium gluconate, and magnesium hydroxide.

30. The composition of claim 29, wherein the Primary Essential Buffer is sodium bicarbonate.

31. The composition of claim 30, wherein the sodium bicarbonate is in an amount from about 400 mg to about 4000 mg.

32. The composition of claim 30, wherein the sodium bicarbonate is in an amount of at least about 800 mg.

33. The composition of claim 29, wherein the Primary Essential Buffer is calcium carbonate.

34. The composition of claim 33, wherein the calcium carbonate is in an amount from about 400 mg to about 4000 mg.

35. The composition of claim 33, wherein the calcium carbonate is in an amount from about 500 mg to about 1000 mg.

36. The composition of claim 33, wherein the calcium carbonate is in an amount of at least about 800 mg.

37. The composition of claim 1, wherein the Secondary Essential Buffer is selected from the group consisting essentially of sodium carbonate, potassium carbonate, trisodium phosphate, tripotassium phosphate, calcium hydroxide, and sodium hydroxide.

38. The composition of claim 1, wherein the gastric fluid pH of the subject is at least 4.6.

39. The composition of claim 1, wherein the gastric fluid pH of the subject is at least 4.8.

40. The composition of claim 1, wherein the gastric fluid pH of the subject is at least 5.6.
41. The composition of claim 1, further comprising at least one flavoring agent.
42. The composition of claim 41, wherein the flavoring agent comprises apple, caramel, meat, chocolate, root beer, maple, cherry, coffee, mint, licorice, nut, butter, butterscotch, peanut butter, aspartame, chocolate, thalmanthin, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.
43. The composition of claim 1, further comprising an anti-foaming agent.
44. The composition of claim 1, further comprising a binder, diluent, lubricant, disintegrant, excipient, colorant, antioxidant, chelating agent, anti-caking agent, moistening agent, preservative, or coating.
45. The composition of claim 1, wherein the composition comprise an inner core comprising a proton pump inhibitor and an optional Primary Essential Buffer.
46. A method of preparing a non-enteric coated solid oral pharmaceutical dosage form comprising active ingredients consisting essentially of a non-enteric coated acid labile proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, free base, or salt thereof; a Primary Essential Buffer; and an optional Secondary Essential Buffer; the method comprises:
- a) blending the proton pump inhibitor, the Primary Essential Buffer, and the optional Secondary Essential Buffer; and

- b) compacting the proton pump inhibitor, the Primary Essential Buffer, and the optional Secondary Essential Buffer into a suspension tablet, chewable tablet, two-part tablet, effervescent powder, or effervescent tablet;

wherein, the proton pump inhibitor is in an amount of approximately 5 mg to approximately 300 mg; and the total amount of the Primary Essential Buffer and the Secondary Essential Buffer is approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor.

### **REMARKS**

Applicant wishes to express his appreciation for the courtesies extended to himself and his representatives, Joseph Mahoney and Dr. Thomas Sharpe, during the March 25, 2002 interview with the Examiner. As stated in the Interview Summary the substance of the interview included: 1. Claim 1 buffer agent will be limited to and quantitative relationship will be introduced; 2. Method claim will be added. Sequential step will be stated and antecedent basis will be pointed out.

As requested by the Examiner, attached is an English translation of the Japanese Patent Application Nos. 05194224 and 05194225.

In the Office Action dated February 1, 2002, claims 1-20 were rejected. In response claims 2-5, and 7-20 have been cancelled, and new claims 21-47 have been added.

Applicants respectfully submit that no new matter has been added by way of the above amendments or by the addition of new claims.

Support in the specification for the amendments made to claim 1 can be found at least as follows:

Claim 1	Support in Specification or Claims	Citation
A solid oral pharmaceutical dosage form that is not enteric-coated or delayed-release, comprising: active ingredients consisting essentially of:		Claim 1 as filed
(a) a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole,		Claim 1 as filed
or an enantiomer, isomer, free base, or salt thereof,	<ul style="list-style-type: none"> <li>• “[F]orm of salts...enantiomers, isomers...”</li> <li>• “[T]he PPIs may be in the free base form...”</li> </ul>	Page 16, line 5 Page 76, line 16
in an amount of approximately 5 mg to approximately 300 mg;	<ul style="list-style-type: none"> <li>• “The dosage range of omeprazole or other proton pump inhibitors such as substituted benzimidazoles and derivatives thereof can range from approximately &lt;2 mg/day to approximately 300 mg/day.”</li> </ul>	Page 18, line 7-8
(b) a Primary Essential Buffer; and		Claim 1 as filed
(c) an optional Secondary Essential Buffer;		Claim 2 as filed
wherein the total amount of the Primary Essential Buffer and the optional Secondary Essential Buffer is in an amount of approximately	<ul style="list-style-type: none"> <li>• “approximately 1 mEq . . . sodium bicarbonate per 2 mg omeprazole with a range of approximately 0.2 mEq . . . to 5 mEq . . . per 2 mg</li> </ul>	Page 20, lines 26-28.

0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor; and	omeprazole.” <ul style="list-style-type: none"> <li>• <b>NB:</b> 0.2 mEq buffer/2 mg PPI = 0.1 mEq buffer/mg of PPI 5 mEq buffer per 2 mg PPI = 2.5 mEq buffer per mg of PPI</li> </ul>	
the composition is dissolvable by gastric fluid upon dissolution oral administration to a subject and upon releases the proton pump inhibitor, the Primary Essential Buffer, and the Secondary Essential Buffer into the gastric fluid elevating pH of the gastric fluid to at least 3.7 from time the proton pump inhibitor comes in contact with the gastric fluid throughout the dwell time; and	<ul style="list-style-type: none"> <li>• “Upon ingestion of the whole tablet, the tablet dissolves and the inner core is dispersed in the stomach where it is absorbed for immediate therapeutic effect.”</li> <li>• “[T]he formulation may be produced in a solid dosage form such as a tablet, capsule or powder with a buffer(s), which disintegrate and reach solution at a rate that exceeds the PPI and thereby provides the Essential pH for protection of the PPI prior to its dissolution and interaction with the acid in the environment.”</li> <li>• “The overall pH of the gastric contents should be kept at least at the pKa + 0.7 (i.e., 3.7) from the time the PPI in solution comes into contact with the gastric acid continuing throughout the dwell time.”</li> </ul>	<p>Page 53, lines 9-11</p> <p>Page 86, lines 19-22</p> <p>Page 85, lines 11-13</p>
the dosage form is selected from the group consisting of suspension tablet, chewable tablet, two-part tablet, effervescent powder, and effervescent tablet.		Claim 8 as filed

Support for amendments to claim 6 can be found at least on page 87, line 28, to page 88, line 1: "[T]hroughout the dwell time, which is typically a minimum of 30 minutes...."

Support for new claim 21 can be found at least on page 8, line 7-8: "The dosage range of omeprazole or other proton pump inhibitors such as substituted benzimidazoles and derivatives thereof can range from approximately <2 mg/day to approximately 300 mg/day."

Support for new claims 22-28 can be found at least in claim 1 as filed.

Support for new claims 22-28, 30, and 33 can be found at least on page 77, Table 8.

Support for new claims 31, 32, 34, and 35 can be found at least page 20, lines 26-28.

Support for new claim 37 can be found at least on page 78, Table 10.

Support for new claim 38 can be found at least on page 78, Table 9.

Support for new claim 39 can be found at least on page 82, line 14.

Support for new claim 40 can be found at least on page 82, line 15.

Support for new claim 41 can be found at least on page 82, line 16.

Support for new claims 42 and 43 can be found at least on page 90, lines 13-14: "apple, caramel, meat, chocolate, root beer, maple, cherry, coffee, mint, licorice, nut, butter, butterscotch, and peanut butter;" and on page 22, lines 12-13; "chocolate, thalmanin, aspartame, root beer or watermelon;" and on page 30, line 6: "peppermint oil, spearmint oil."

Support for new claim 44 can be found at least on page 13, line 27.

Support for new claim 45 can be found at least on page 25, lines 16-20: "Dry oral formulations can contain excipients such as binders...diluent...disintegrating agents...and lubricating agents...."; and on page 25, lines 24-25: "excipients, colorants, diluents, buffering agents, moistening agents, preservatives..."; and on page 21, lines 23-24: "preservatives and antioxidants...anti-caking agents, coating agents, and chelating agents."



Support for new claim 46 can be found at least on pages 116-120, where numerous examples of two-part tablets are provided.

Support for new claim 47 can be found at least as follows:

Claim 47	Support in Specification or Claims	Citation
A method of preparing a non-enteric coated solid oral pharmaceutical dosage form comprising active ingredients consisting essentially of a non-enteric coated acid labile proton pump inhibitor (PPI) selected from the group consisting of omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, free base, or salt thereof; a Primary Essential Buffer; and an optional Secondary Essential Buffer; the method comprises:		Claim 16, as filed; See claim 1 above
blending the proton pump inhibitor, the Primary Essential Buffer, and the optional Secondary Essential Buffer; and	<ul style="list-style-type: none"> <li>• See Table 13</li> <li>• "Thoroughly blend the powder..."</li> </ul>	Page 107, line 1 Page 107, line 8
compacting the proton pump inhibitor, the Primary Essential Buffer, and the optional Secondary Essential Buffer into a suspension tablet, chewable tablet, two-part tablet, effervescent powder, or	<ul style="list-style-type: none"> <li>• "Compressed tablets are solid dosage forms prepared by compacting a formulation containing an active ingredient...."</li> </ul>	Page 25, lines 11-12

effervescent tablet;		
wherein, the proton pump inhibitor is in an amount of approximately 5 mg to approximately 300 mg; and the total amount of the Primary Essential Buffer and the Secondary Essential Buffer is approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor.		See claim 1 above

***I. Rejection Under 35 U.S.C. § 102(b)***

Claims 1-20 were rejected under 35 U.S.C. § 102(b) as being anticipated by JP05194224 or JP05194225, by Oishi, *et al.* The Office Action stated that the claim language as presented reads on the references since “comprising” is an open-ended term.

The claims have been amended to better define the invention. In particular, the non-enteric coated or non-delayed-release pharmaceutical dosage form comprises active ingredients consisting essentially of a non-enteric coated proton pump inhibitor, a Primary Essential Buffer, and a Secondary Essential Buffer. The proton pump inhibitor is in an amount of approximately 5 mg to approximately 300 mg; and the total amount of the Primary Essential Buffer and the Secondary Essential Buffer is approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor. As JP05194224 and JP05194225 fail to disclose each and every element of the amended present claimed invention and fail to sufficiently describe the claimed invention to have placed the public in possession of it, the applicant submits that anticipation cannot be found. It is therefore respectfully requested that the rejection of Claims 1-20 under 35 U.S.C. § 102(b) be withdrawn.

## **II. Rejections Under 35 U.S.C. § 103(a)**

Claims 1-20 were rejected under 35 U.S.C. § 103(a) as being unpatentable over JP05194224 or JP05194225, by Oishi, *et al.* The Office Action noted that the above § 102 rationale applies, and stated in “patent law where patentability is based on a change of pKa or pH in a pharmaceutical composition, such change must be ‘critical’ and it must lead to a new and unexpected result.”

The claims have been amended to better define the invention. In particular, the non-enteric coated or non-delayed-release pharmaceutical dosage form comprises active ingredients consisting essentially of a non-enteric coated proton pump inhibitor, a Primary Essential Buffer, and a Secondary Essential Buffer. The proton pump inhibitor is in an amount of approximately 5 mg to approximately 300 mg; and the total amount of the Primary Essential Buffer and the Secondary Essential Buffer is approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor. As JP05194224 and JP05194225 do not contain all the elements of the amended present claimed invention, and thus the claimed invention can be distinguished over the combination of the cited references, reconsideration and withdrawal of this rejection is respectfully requested.

## **III. Rejections Under 35 U.S.C. § 112, Second Paragraph**

Claims 1-20 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular the Office Action stated:

1. “The claims are indefinite by reference to an environment in a liquid phase which are all variable because the relationship of the degradation of PPI by gastric acid in such an environment is not based on any known standard.”

2. "All claims are hybrid claims."
3. "There is no therapeutically effective amount of a composition which can be prepared for shelf-storage."
4. "What do '0.7 log,' and '1.0 log' mean?"
5. "What are 'a suspension tablet,' 'two-part tablet or capsule'? Are they art recognized terms?"
6. "The word 'enteral' is not understood."
7. "What do[es] 'a rapid acting buffer,' 'essential pH of a dose,' 'typical set of storage condition' mean?"

In response, the claims have been amended to better define the invention. In particular the following is respectfully brought to the Examiner's attention:

- a. Reference to "a liquid phase in an environment" has been deleted.
- b. The amount of the proton pump inhibitor is now defined in an amount of approximately 5 mg to approximately 300 mg, and the amount of the Primary Essential Buffer and the optional Secondary Essential Buffer have also been defined to be in a total amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor.
- c. The claims containing the phrase "0.7 log," and "1.0 log" have been cancelled, without prejudice.
- d. Regarding the phrase "suspension tablet," the Examiner's attention is respectfully directed to page 23, lines 24-26, where it states:

“The term ‘suspension tablets’ as used herein refers to compressed tablets which rapidly disintegrate after they are placed in water, and are readily dispersible to form a suspension containing a precise dosage of the PPI.”

From this disclosure the Applicant respectfully contends that one skilled in the art would recognize the meets and bounds of the phrase “suspension tablet.”

- e. Regarding the phrase “two-part tablet or capsule,” the Examiner’s attention is respectfully directed to the following disclosure in the specification where several examples of “two-part tablets” are provided:

- (i) Page 116, “Formulation 28: Omeprazole Two-Part Tablet,”
- (ii) Page 117, “Formulation 29: Lansoprazole Two-Part Tablet,”
- (iii) Page 118, “Formulation 30: Pantoprazole Two-Part Tablet,” and  
“Formulation 31: Omeprazole or esomeprazole Two-Part tablet,”
- (iv) Page 119, “Formulation 32: Lansoprazole Two-Part tablet,” and  
“Formulation 33: Pantoprazole Two-Part tablet,”
- (v) Page 120, “Formulation 34: Omeprazole 20 mg Two-Part Tablet,”  
“Formulation 35: Lansoprazole 30 mg Two-Part Tablet,” “Formulation  
36: Rabeprazole 20 mg Two-Part Tablet,” and “Formulation 37:  
Omeprazole Two-Part Tablet.”

From this disclosure the Applicant respectfully contends that one skilled in the art would recognize the meets and bounds of the phrase “two-part tablet or capsule.”

- f. Regarding the term “enteral,” the Examiner’s attention is respectfully directed to page 18, lines 12-15, where it states:

“A pharmaceutical formulation of the proton pump inhibitors utilized in the present invention can be administered orally or enterally to the patient. This can be accomplished, for example, by administering the solution via a nasogastric (ng) tube or other indwelling tubes placed in the GI tract.”

From this disclosure the Applicant respectfully contends that one skilled in the art would recognize the meets and bounds of the term “enteral.” Additionally, one skilled in the art would recognize that the term “enteral” means “[w]ithin, or by way of, the intestine or gastrointestinal tract, especially as distinguished from parenteral.” (See Stedman’s Medical Dictionary, 25<sup>th</sup> Edition, Williams & Wilkins (William R. Hensyl ed., 1990)).

- g. Reference to the phrases “a rapid acting buffer,” “essential pH of a dose,” and “typical set of storage conditions” has been deleted.

Reconsideration and withdrawal of this 35 U.S.C. § 112, second paragraph, rejection is respectfully requested.

#### ***IV. Rejections Under 35 U.S.C. § 112, First Paragraph***

##### ***(i) Claims 1-20***

Claims 1-20 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or which it is most nearly connected, to make and/or use the invention. The Office Action stated among other things, that the combinations and permutations derived therefrom are enormous which is beyond the enabling disclosure, and that such a composition cannot be prepared independently outside of a living subject and stored on the shelf.

The claims have been amended to better define the invention. In particular, the amount of the proton pump inhibitor has been defined to be in an amount of approximately 5 mg to approximately 300 mg, and the amount of the Primary Essential Buffer and the optional Secondary Essential Buffer has been defined to be in a total amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor.

Reconsideration and withdrawal of this 35 U.S.C. § 112, first paragraph, rejection is respectfully requested.

*(ii) Claim 16*

Claim 16 was rejected under 35 U.S.C. § 112, first paragraph, because as stated by the Office Action, there was no quantitative relationship among parts a, b, c, d.

Claim 16 has been cancelled and reconsideration and withdrawal of this rejection is therefore respectfully requested.

*V. Rejection Under 35 U.S.C. § 101, Same Invention Type Rejection*

Claims 1-20 were provisionally rejected as claiming the same invention as that of claims of copending Application No. 09/481,207. The claims have been amended to better define the invention. In particular, the non-enteric coated or non-delayed-release pharmaceutical dosage form comprises active ingredients consisting essentially of a non-enteric coated proton pump inhibitor, a **Primary Essential Buffer**, and a **Secondary Essential Buffer**. Withdrawal of this rejection is requested.

*VI. Obviousness-type Double Patenting Rejection*

Claims 1-20 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over copending Application No.

09/481,207. Applicant respectfully submits a terminal disclaimer under 37 CFR 1.321, and fee, to obviate this provisional double patenting rejection over copending Application No.

09/481,207. Withdrawal of this rejection is requested.

### CONCLUSION

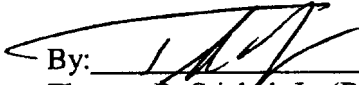
With entry of the above Amendment and in view of the foregoing remarks, it is respectfully submitted that claims 1, 6, and 21-46 are in condition for allowance.

None of Applicant's amendments or cancellations are to be construed as dedicating any such subject matter to the public, and Applicants reserve all rights to pursue any such subject matter in this or a related patent application.

Also submitted below, on a separate page titled "Version with Marking to Show Changes Made to the Claims," is a marked-up copy of prior pending claims. It is respectfully submitted in view of the foregoing Amendment and Remarks that all of the objections and rejections in the Office Action dated February 1, 2002 have been overcome and should be withdrawn. Applicant respectfully requests early and favorable notification to that effect. The Examiner is encouraged to contact the undersigned with any questions or to otherwise expedite prosecution.

Respectfully submitted,

Dated: July 1, 2002

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**Version with Marking to Show Changes Made to the Claims**

1. (Amended) A solid oral pharmaceutical dosage form that is not enteric-coated or delayed-release, comprising active ingredients consisting essentially of:

a) a non-enteric coated proton pump inhibitor (PPI) selected from a group consisting of omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, pariprazole and leminoprazole, or an enantiomer, isomer, free base, or salt thereof, in an amount of approximately 5 mg to approximately 300 mg; and

b) a Primary Essential Buffer; and [present in an amount sufficient such that when the dosage form is placed in a liquid phase in an environment, the Primary Essential Buffer maintains the pH of the environment at a value greater than the pKa of the PPI for a time sufficient to substantially avoid acid degradation of the PPI in the environment.]

(c) an optional Secondary Essential Buffer;

wherein the total amount of the Primary Essential Buffer and the optional Secondary Essential Buffer is in an amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor; and

the composition is dissolvable by gastric fluid upon oral administration to a subject and upon dissolution releases the proton pump inhibitor, the Primary Essential Buffer, and the Secondary Essential Buffer into the gastric fluid elevating pH of the gastric fluid to at least 3.7 from time the proton pump inhibitor comes in contact with the gastric fluid throughout the dwell time; and

the dosage form is selected from the group consisting of suspension tablet, chewable tablet, two-part tablet, effervescent powder, and effervescent tablet.

6. (Amended) The dosage form as recited in Claim 1, [5] wherein the dwell time is equal to or less than about 30 minutes.

(51) Int. Cl. <sup>5</sup>	Identifying symbols	Internal filing number	FI	Technical designations
A 61 K 31/44	ACL		7252-4C	
47/04		Z	7433-4C	
47/16		J	7433-4C	
//(A 61 K 31/44				
31:195)			8413-4C	
		Request for examination: Not filed		Number of claims: 1 (7 pages total)

(21) Application number	HEI4-273690	(71) Applicant	000006725 Yoshitomi Pharmaceutical Industries, Ltd. Osaka-fu, Osaka-shi, Chuo-ku, Hirano-machi 2-chome, 6-9
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(54) [Title of invention] Stabilized antiulcer agent-containing preparation

(57) [Abstract]

[Constitution] A stabilized antiulcer agent-containing preparation distinguished in that a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound, which has an antiulcer effect and is unstable in acid, is compounded with aluminum glycinate and a buffering agent as stabilizers.

[Benefit] It was discovered that when benzimidazole compounds unstable in acid are compounded and with a combination of aluminum glycinate and buffering agent, the benzimidazole compound is markedly stabilized, and coloration does not take place. Thus, the use of these stabilizers allows a stabilized antiulcer agent-containing preparation to be obtained.

**[Claims]**

**[Claim 1]** A stabilized antiulcer agent-containing preparation distinguished in that a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound, which has an antiulcer effect and is unstable in acid, is compounded with aluminum glycinate and a buffering agent as stabilizers.

**[Detailed description of the invention]****[0001]**

**[Field of industrial application]** The present invention relates to stabilized antiulcer agent-containing preparations.

**[Prior art and problems to be solved by the invention]** 2-[(2-pyridyl)methylsulfinyl]benzimidazole compounds having an  $H^+-K^+$  ATPase inhibitory effect (hereinafter also referred to simply as benzimidazole compounds) are useful as peptic ulcer treatment agents that strongly suppress gastric acid secretion. Because their action is strong and sustained, they have received attention as next-generation peptic ulcer treatment agents to replace histamine  $H_2$  receptor antagonists such as cimetidine. In particular, the gastric acid secretion suppressant effect of the benzimidazole compounds described in Unexamined Patent Publications SHO54-141783, SHO61-50978, HEI1-6270, etc., is strong, and their clinical utility has been confirmed. However, these benzimidazole compounds have poor stability, being unstable against temperature, humidity and light when in a solid state, and rapidly disintegrating and coloring when in an acidic to neutral aqueous solution. Furthermore, in pharmaceutical preparations such as tablets, pellets, granules, capsules and powders, they are affected by other ingredients in the formula, becoming unstable and undergoing chronological loss in content and discoloration. Moreover, among these preparations, when tablets or granules are provided with a coating, the compounding properties with enteric substrates (cellulose acetate phthalate, hydroxypropyl methyl cellulose, hydroxymethyl cellulose acetate succinate, methacrylic acid/acrylic acid copolymer, etc.) is poor, and loss in content and coloration occur. In this way, while production of oral preparations of benzimidazole compounds requires compounding with other ingredients and an enteric coating, because this has an adverse effect on stability as described above, creating such preparations was difficult. Thus, to make these compounds into preparations for oral administration, it is necessary to suitably stabilize them. Many stabilizers and stabilization methods have already been studied for obtaining a stable benzimidazole compound preparation having an antiulcer effect, such as the method of compounding with alkaline reactive compounds (Unexamined Patent Publication SHO62-258320), the method of compounding with magnesium or calcium basic inorganic salts (Unexamined Patent Publication SHO62-277322), the method of compounding with magnesium oxide and mannitol (Unexamined Patent Publication HEI2-22225), etc., but the development of

more useful stabilized preparations has been desired.

[0002]

[Means of solving the problems] The inventors, in view of this situation, as a result of concerted studies using various basic substances for the purpose of stabilizing benzimidazole compound-containing compositions, discovered that the aforementioned problem can be solved through the combined use of aluminum glycinate and buffering agent, thereby completing the present invention. That is, the present invention relates to a stabilized antiulcer agent-containing preparation distinguished in that a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound, which has an antiulcer effect and is unstable in acid, is compounded with aluminum glycinate and a buffering agent as stabilizers. In the present invention, the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound which has an antiulcer effect and is unstable in acid is specifically a compound as described in the aforementioned patent publications and the like, including for instance omeprazole (5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole), lansoprazole (2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole) or 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methylsulfinyl]-1H-benzimidazole sodium salt, etc.

[0003] The buffering agents used in the present invention include sodium tartrate, sodium acetate, sodium hydrogen carbonate, sodium carbonate, sodium polyphosphate, dipotassium hydrogen phosphate, sodium pyrophosphate, disodium hydrogen phosphate, trisodium phosphate and tripotassium phosphate; of these, disodium hydrogen phosphate is preferable. The compounding quantities in the present invention are desirably in the range of 0.1 to 20 parts by weight aluminum glycinate and 0.01 to 20 parts by weight buffering agent per 1 part by weight benzimidazole compound, but are not limited thereto. The inventive stabilizers may be added together with commonly used pharmaceutical additives, for instance excipients such as lactose, mannitol, corn starch and crystalline cellulose, binding agents such as hydroxypropyl cellulose, disintegrants such as low-substituted hydroxypropyl cellulose, carboxymethyl starch sodium (trade name: Explotab, Kimura Sangyo), carboxymethyl cellulose calcium and -starch, surfactants such as sodium lauryl sulfate and Tween 80 (trade name), lubricants such as magnesium stearate and talc, etc.

[0004] The inventive composition is obtained by mixing a benzimidazole compound, aluminum glycinate and a buffering agent, as well as the aforementioned additives and water as required, uniformly in a kneader. For the mixing method, the benzimidazole compound may be mixed with aluminum glycinate and buffering agent first and then mixed with additives, or one may mix the benzimidazole compound with additives and then add stabilizers thereto: any method may be

used so long as ultimately the stabilizers are in uniform contact with the benzimidazole compound. The obtained mixture is made into small granules by a wet granulation method, and are then tableted to obtain a base tablet for a tablet preparation. Alternately, one can make granules using an extrusion granulator and then prepare core granules for a granule preparation using a Marumerizer (made by Fuji Paudal).

[0005] The base tablets or core granules obtained in this manner can be covered with an enteric coating to make enteric preparations, but to avoid adverse effects from the enteric coating, the base tablet or core granules are covered with 1 to 2 layers of undercoating. Undercoating agents include hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, etc.; the aforementioned aluminum glycinate, aluminum hydroxide, and if required, the aforementioned buffering agents may also be added to the undercoating layers. Moreover, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid/acrylic acid copolymer (trade name: Eudragit) and the like may be used for the enteric undercoating. In the above manner, it is possible to obtain enteric tablets or granules, which are suitable preparations for oral administration; moreover, the granules can be filled into capsules to make a capsule preparation. Preparations obtained in this manner exhibit excellent stability, undergoing little change in appearance and almost no loss in content even when stored for long periods. The inventive preparations have excellent gastric acid secretion suppressant effect and antiulcer effect, as well as having low toxicity, and thus can be used for treatment of peptic ulcers, etc., in mammals, including humans.

[0006]

[Embodiment examples] Below, the invention is explained in greater detail by presenting experiment examples and embodiment examples; the present invention is however not limited thereto.

#### Experiment example 1

100 mg omeprazole, aluminum glycinate and the buffering agent disodium hydrogen phosphate ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ) were dispersed in 20 ml water and stored at 25°C to examine chronological change in appearance of the white suspension. Furthermore, chronological change in appearance at 25°C of control liquids not containing either the aluminum antacid or the buffering agent was observed.

[0007]

[Table 1]

Table 1

		Added substance	(mg)	Change in appearance at 25°C		
				1 day	3 days	7 days
Present invention		Aluminum glycinate	100	White	White	White
		Na <sub>2</sub> HPO <sub>4</sub> 12H <sub>2</sub> O	30			
		Aluminum glycinate	100	White	White	White
		Na <sub>2</sub> HPO <sub>4</sub> 12H <sub>2</sub> O	100			
Control		None	—	Light purple	Purple	Blackish purple
	Antacid	Aluminum glycinate	200	Faint purple	Brown	Brown
		Aluminum hydroxide	200	Purple	Purple	Purple
		Magnesium carbonate	200	White	Faint brown	Light brown
		Synthetic hydrotalcite	200	White	Faint gray	Light brown
	Buffering agent	Na <sub>2</sub> HPO <sub>4</sub> 12H <sub>2</sub> O	200	Light brown	Light brown	Light brown
		Sodium tartrate	200	Light purple	Purple	Purple
		Sodium acetate	200	Faint brown	Light purple	Light purple
		Sodium hydrogen carbonate	200	White	Faint brown	Light purple
		Sodium polyphosphate	200	Faint brown	Faint brown	Light brown
		Dipotassium hydrogen phosphate	200	Light brown	Light brown	Light brown
		Sodium pyrophosphate	200	Faint brown	Faint brown	Light brown

[0008] The results were that coloration of omeprazole tended not to occur when aluminum glycinate and buffering agent were used in combination as compared to using either alone, showing that omeprazole was stabilized through the combined use.

[0009] Embodiment example 1

The following composition was placed in a kneader and mixed for approximately 20 minutes, after which a suitable quantity of water was added thereto and the mixture was kneaded and granulated in an extrusion granulator (screen diameter 1.0 mm), after which spherical granules were obtained with a Marumerizer (Fuji Paudal). These granules were dried for 30 minutes at a supply air temperature of 50°C in a fluidized dryer, and granules of 14 to 24 mesh were obtained using a sieve.

Omeprazole	5.0 mg
Aluminum glycinate	5.0 mg
Sodium pyrophosphate	2.0 mg
Crystalline cellulose	4.0 mg
Low-substituted hydroxypropyl cellulose	4.0 mg
Hydroxypropyl cellulose	0.5 mg

Mannitol	54.5 mg
Total	75.0 mg

## [0010] Embodiment example 2

Granules were obtained from the following composition in a manner analogous to embodiment example 1. The disodium hydrogen phosphate ( $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ ) was compounded after dissolving in purified water.

Omeprazole	5.0 mg
Aluminum glycinate	5.0 mg
$\text{Na}_2\text{HOP}_4 \cdot 12\text{H}_2\text{O}$	1.5 mg
Crystalline cellulose	4.0 mg
Low-substituted hydroxypropyl cellulose	4.0 mg
Hydroxypropyl cellulose	0.5 mg
Mannitol	55.0 mg
Total	75.0 mg

## [0011] Embodiment example 3

The granules obtained in embodiment example 2 were provided with coatings of the following composition to obtain enteric granules. Undercoatings 1 and 2 were applied in a fluidized spray dryer (Ogawara) at a supply air temperature of 75°C, exhaust temperature 55°C, and the enteric coating was applied at a supply air temperature of 65°C, exhaust temperature 50°C.

Granules from embodiment example 2	75.0 mg
Undercoating 1	
Hydroxypropyl methyl cellulose	3.5 mg
Aluminum glycinate	1.4 mg
$\text{Na}_2\text{HOP}_4 \cdot 12\text{H}_2\text{O}$	0.1 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	5.5 mg
Undercoating 2	
Hydroxypropyl methyl cellulose	3.5 mg
Titanium oxide	2.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	6.5 mg



**Enteric coating**

Hydroxypropyl methyl cellulose phthalate	10.7 mg
Cetanol	0.5 mg
Talc	1.8 mg
Methylene chloride	(33.0 mg)
Ethanol	(86.0 mg)
Purified water	(33.0 mg)
Total	13.0 mg

The obtained omeprazole enteric granules had excellent elution properties and were stable even when stored under heated and humidified conditions.

**[0012] Embodiment example 4**

Of the components indicated below, lansoprazole, aluminum glycinate, mannitol, starch, sodium lauryl sulfate and hydroxypropyl cellulose were mixed uniformly, sodium pyrophosphate dissolved in a suitable quantity of purified water was added thereto, kneading was carried out, and then the mixture was dried in a fluidizer dryer for 30 minutes at 50°C. The dried granulate was sorted with a 24 mesh sieve, magnesium stearate was added to it and mixed, and then tablets (base tablets) were produced at 135 mg per tablet using a rotary tablet machine.

Omeprazole	20.0 mg
Aluminum glycinate	20.0 mg
Sodium pyrophosphate	1.0 mg
Mannitol	71.7 mg
-starch	20.0 mg
Sodium lauryl sulfate	0.3 mg
Hydroxypropyl cellulose	1.0 mg
Magnesium stearate	1.0 mg
Total	135.0 mg

**[0013] Embodiment example 5**

The tablets (base tablets) obtained in embodiment example 4 were provided with coatings of the following composition to obtain enteric tablets. For undercoatings 1 and 2, coating was carried out using a Hi-Coater (Freund Industrial) at a supply air temperature of 70°C, exhaust temperature 40°C, pan speed 13 rpm. For the enteric coating, coating was carried out at a supply air temperature of 55°C, exhaust air temperature 37°C.

Tablets from embodiment example 4 135.0 mg

**Undercoating 1**

Hydroxypropyl methyl cellulose	1.5 mg
Aluminum glycinate	0.35 mg
Na <sub>2</sub> HPO <sub>4</sub> 12H <sub>2</sub> O	0.05 mg
Purified water	(23.0 mg)
Total	1.9 mg
Undercoating 2	
Hydroxypropyl methyl cellulose	3.1 mg
Titanium oxide	1.0 mg
Purified water	(56.0 mg)
Total	4.1 mg
Enteric coating	
Hydroxypropyl methyl cellulose phthalate	3.1 mg
Cetanol	0.2 mg
Talc	0.2 mg
Ethanol	(35.0 mg)
Purified water	(10.0 mg)
Total	3.5 mg
Grand total	144.5 mg

[0014] Embodiment example 6

Core granules of the following formula were produced in accordance with embodiment example 1. The sodium pyrophosphate used as stabilizer was compounded after diluting in purified water. Aluminum glycinate and Na<sub>2</sub>HPO<sub>4</sub> 12H<sub>2</sub>O were compounded into undercoating 1 in order to prevent compounding change between the enteric film and the omeprazole in the core granules. The film coatings were applied using a fluidized spray dryer (Ogawara). Undercoatings 1 and 2 were applied at a supply air temperature of 75°C, exhaust temperature 55°C, and the enteric coating was applied at a supply air temperature of 55°C, exhaust temperature 40°C.

Core granules

Omeprazole	5.0 mg
Aluminum glycinate	10.0 mg
Sodium pyrophosphate	2.0 mg
Crystalline cellulose	4.0 mg
Low-substituted hydroxypropyl cellulose	4.0 mg
Hydroxypropyl cellulose	0.5 mg
Mannitol	44.5 mg

Total	70.0 mg
Undercoating 1	
Hydroxypropyl methyl cellulose	3.2 mg
Aluminum glycinate	1.2 mg
Na <sub>2</sub> HOP <sub>4</sub> 12H <sub>2</sub> O	0.1 mg
Talc	0.5 mg
Purified water	(60.0 mg)
Total	5.0 mg
Undercoating 2	
Hydroxypropyl methyl cellulose	3.5 mg
Titanium oxide	1.0 mg
Talc	0.5 mg
Purified water	(65.0 mg)
Total	5.0 mg
Enteric coating	
Eudragit L-30D-55 (solid content)	15.0 mg
Polyethylene glycol 6000	1.3 mg
Tween 80	0.7 mg
Talc	3.0 mg
Purified water	(50.0 mg)
Total	20.0 mg
Grand total	100.0 mg

## [0015] Reference example 1

Tablets (base tablets) were prepared using the following formula in accordance with embodiment example 4.

Omeprazole	20.0 mg
Mannitol	93.2 mg
-starch	20.0 mg
Sodium lauryl sulfate	0.3 mg
Hydroxypropyl cellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

The obtained tablets (base tablets) were provided with the undercoating 2 and enteric coating from embodiment example 5 to obtain enteric tablets.

## [0016] Reference example 2

Tablets (base tablets) were prepared using the following formula in accordance with embodiment example 4.

Omeprazole	20.0 mg
Aluminum glycinate	20.0 mg
Mannitol	73.2 mg
-starch	21.0 mg
Sodium lauryl sulfate	0.3 mg
Hydroxypropyl cellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

The obtained tablets (base tablets) were provided with the film coating of embodiment example 5 to obtain enteric tablets.

## [0017] Experiment example 2

The base tablets obtained in embodiment example 4, the enteric tablets obtained in embodiment example 5, the base tablets and enteric tablets obtained in reference example 1 and the base tablets and enteric tablets obtained in reference example 2 were placed into glass bottles, sealed under conditions of 60°C or left open under conditions of 40°C, 75% RH, and in each case left for two weeks. The results of change in appearance are indicated in Table 2.

[0018]

[Table 2]

Table 2

	At time of preparation	60°C sealed	40°C, 75% RH open
Embodiment example 4 (tablets)	White	White	White
Embodiment example 5 (enteric tablets)	White	White	White
Reference example 1 (base tablets)	Faint brown	Light brown	Light brown
(enteric tablets)	White	Faint brown	Light brown
Reference example 2 (base tablets)	Light brown	Light brown	Light brown
(enteric tablets)	Faint brown	Light brown	Light brown

[0019] As is clear from the results shown in Table 2, by compounding aluminum glycinate and buffering agent, change in appearance was markedly improved.

[0020]

[Benefits of the invention] When aluminum glycinate or buffering agent were each used alone

and compounded with a benzimidazole compound, as is clear from the experimental results, no stabilization effect was obtained, while when they were used together, it was found that the benzimidazole compounds were markedly stabilized. Thus, the combined use of aluminum glycinate and buffering agent allows a stabilized antiulcer agent-containing preparation to be obtained.

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## SPECIFICATION

### (54) [Title of the Invention]

Preparation Containing Stabilized Antiulcer Agent

### (57) [Abstract]

[Constitution] A preparation containing stabilized antiulcer agent, formed by blending amino acid, amino acid salt or amino acid alkali salt as stabilizer, along with buffering agent, with a benzimidazole compound that has antiulcer action and is not stable in acids.

[Effect] It was discovered that benzimidazole compounds have excellent stability and do not discolor when amino acid, amino acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, are blended with benzimidazole compound that is not stable in acid. Preparations containing stabilized antiulcer agent are obtained by using these stabilizers.

### [Claims]

[Claim 1] A preparation containing stabilized antiulcer agent, formed by blending amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, with a benzimidazole compound that has antiulcer action and is not stable in acids.

[Claim 2] The preparation according to Claim 1, wherein the benzimidazole compound is 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound.

[Claim 3] The preparation according to Claim 1, wherein the benzimidazole compound is omeprazole, lansoprazole, or 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methylsulfinyl]-1H-benzimidazole sodium salt.

[Claim 4] The preparation according to Claim 1, wherein the amino acid, amino acid salt or amino acid alkali salt is glycine, glycine hydrochloride, L-alanine, DL-alanine, L-threonine, DL-threonine, L-isoleucine, L-valine, L-phenylalanine, L-glutamic acid, L-glutamic acid hydrochloride, L-glutamic acid sodium salt, L-asparaginic acid, L-asparaginic acid sodium salt, L-lysine or L-lysine-L-glutamate, and the buffer is

phosphoric acid alkali metal salt, sodium tartrate, sodium acetate, sodium carbonate, sodium bicarbonate, sodium polyphosphate, sodium pyrophosphoric acid, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium carbonate, aluminum hydroxide-sodium bicarbonate coprecipitate or aluminum glycinate.

[Claim 5] The preparation according to Claim 1, which is a tablet, granule or capsule.

[Claim 6] The preparation according to Claim 1, wherein the amino acid, amino acid acid salt or amino acid alkali salt is glycine, glycine hydrochloride, L-alanine, DL-alanine or L-glutamic acid sodium salt, and the buffer is disodium hydrogen phosphate.

[Claim 7] The preparation according to Claim 1, wherein the benzimidazole compound, the amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, and the buffering agent are blended to produce a core tablet, which is coated with 1-2 layers of undercoating, and an enteric coating is then applied thereupon.

[Claim 8] The preparation according to Claim 1 and Claim 7, wherein acid-controlling substance having a buffering action and, as necessary, buffering agent are contained in the undercoating layer.

[Claim 9] The preparation according to Claim 8, wherein the acid-controlling substance having buffering action in the undercoating layer is magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium silicate, synthetic hydrotalcite, aluminum hydroxide, aluminum glycinate or aluminum hydroxide-sodium bicarbonate coprecipitate, and the buffering agent is sodium tartrate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, dipotassium hydrogen phosphate, sodium pyrophosphate, disodium hydrogen phosphate, trisodium phosphate or tripotassium phosphate.

[Claim 10] The preparation according to Claim 1 and Claim 7, wherein the enteric coating is cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetosuccinate, polyvinyl acetate phthalate, carboxymethylethylcellulose or methacrylic acid-acrylic acid copolymer.



## **[Detailed Description of the Invention]**

[0001]

[Field of industrial utilization] The present invention relates to a preparation containing stabilized antiulcer agent

[Prior art and problems to be solved by the invention] Benzimidazole compounds which have  $H^+-K^+$  ATPase inhibition action are useful as digestive ulcer treatments that strongly inhibit stomach acid secretion. This action is strong and persistent, and so these compounds are receiving attention as next-generation digestive ulcer treatments that will supplant histamine  $H_2$  receptor antagonist such as cimetidine. In particular, the benzimidazole compounds described in Japanese Unexamined (Kokai) Patent Application No. Sho 54[1979]-141783, Japanese Unexamined (Kokai) Patent Application No. Sho 61[1986]-60978 and Japanese Unexamined (Kokai) Patent Application No. Hei 1[1989]-6270 have particularly strong stomach acid secretion inhibitory actions, and their clinical effectiveness has been confirmed. However, these benzimidazole compounds have poor stability, and when in solid form, they are unstable with respect to moisture, heat and light. In addition, the substances rapidly decompose and become extremely discolored in acidic to neutral aqueous solutions. With preparations such as tablets, fine powders, granules, capsules and dispersions, the compounds are influenced by other components of the preparation formula and become unstable, leading to a decrease in content and discoloration over time. Among these preparations, when the compounds are coated to produce granules, they have poor compounding properties with respect to enteric bases (cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, polyvinyl acetate phthalate, and methacrylic acid acrylic acid copolymer), and suffer content decrease and discoloration. When an oral preparation is to be manufactured in this manner using benzimidazole compound, in addition to problems arising from the need for compounding with other components and the use of enteric base coatings, there are also difficulties with formulation due to the detrimental influences on stability as described above. Consequently, it is necessary to appropriately stabilize these compounds when they are to be formulated in oral dosage forms. A great deal of research has been carried out on stabilizers and stabilization methods for obtaining preparations with stable benzimidazole compounds having antiulcer action; for example, methods that involve blending alkali reaction compounds (Japanese Unexamined (Kokai) Patent Application No. Sho 62[1987]-258320), methods

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that involve the blending of basic inorganic salts of magnesium or calcium (Japanese Unexamined (Kokai) Patent Application No. Sho 62[1987]-277322), and methods that involve the blending of magnesium oxide and mannitol (Japanese Unexamined (Kokai) Patent Application No. Hei 2[1990]-22225).

[0002]

[Means for solving the problems] The inventors of the present invention et al., in light of this state of affairs, carried out painstaking investigations concerning various stabilizers with the objective of stabilizing compositions that contain benzimidazole compounds. The present invention was thus perfected upon the discovery that the above problems can be eliminated by means of using amino acids and buffers in conjunction. Specifically, the present invention relates to a preparation containing stabilized antiulcer agent, formed by blending amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, with a benzimidazole compound having antiulcer action that is not stable in acids. In the present invention, examples of benzimidazole compounds that have antiulcer action and are not stable in acid include 2-[(2-pyridyl)methylsulfinyl]benzimidazole compounds, and specifically, the compounds described in the various aforementioned publications; for example, omeprazole (5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole), lansoprazole (2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole) or 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methylsulfinyl]-1H-benzimidazole sodium salt.

[0003] In the present invention, examples of amino acids, amino acid acid salts and amino acid alkali salts include glycine, glycine hydrochloride, L-alanine, DL-alanine, L-threonine, DL-threonine, L-isoleucine, L-valine, L-phenylalanine, L-glutamic acid, L-glutamic acid hydrochloride, L-glutamic acid sodium salt, L-asparaginic acid, L-asparaginic acid sodium salt, L-lysine and L-lysine-L-glutamic acid salt. These substances can be used in conjunction, but it is preferable to use glycine, glycine hydrochloride, L-alanine, DL-alanine or L-glutamic acid sodium salt. The term "buffer" refers to an additive that controls the pH in the weakly alkaline range of 8-9. Examples include phosphoric acid alkali metal salts (disodium hydrogen phosphate, dipotassium hydrogen phosphate, trisodium phosphate, tripotassium phosphate, sodium dihydrogen phosphate and potassium dihydrogen phosphate), sodium tartrate, sodium acetate, sodium carbonate, sodium bicarbonate, sodium polyphosphate, sodium pyrophosphate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate,

magnesium silicate, calcium carbonate, aluminum hydroxide-sodium bicarbonate coprecipitate (product name, Cumulite; Kyowa Chemical Industry Co.) and aluminum glycinate (product name Glycinal; Kyowa Chemical Industry Co.). These substances can be used individually or in conjunction, but disodium hydrogen phosphate is preferred. In addition, the preferred blend amounts of these substances are in the ranges of 0.01-10 parts by weight of amino acid and 0.01-10 parts by weight of buffer with respect to 1 part by weight of benzimidazole compound. However, amounts are not restricted to these ranges. The stabilizer of the present invention can be added together with additives that are commonly used in drugs, for example, mannitol, corn starch, crystalline cellulose and other excipients, hydroxypropylcellulose and other binders, hydroxypropylcellulose with a low degree of substitution, carboxymethylstarch sodium (product name Explotab; Kimura Sangyo), carboxymethylcellulose calcium and other disintegration agents, sodium laurylsulfate, Tween 80 (product name) and other surfactants, and magnesium stearate, talc and other glazes.

[0004] The composition of the present invention is obtained by using a kneader to uniformly blend the benzimidazole compound, the amino acid, amino acid acid salt or amino acid alkali salt stabilizer, the buffering agent, the above additives, and water, used as necessary. However, the blending method, for example, can involve blending the benzimidazole compound with the amino acid, amino acid acid salt or amino acid alkali salt and buffering agent to produce a material, which is then blended with the additives. Alternatively, a method can be used wherein the benzimidazole compound is blended with the additives to produce a material to which the stabilizer is added, followed by bringing about uniform contact between the stabilizer and benzimidazole compound. The resulting mixture is then finely granulated with a wet granulator, and the material is then subjected to tabletization to produce uncoated tablets for tablet production. Alternatively, the material can be granulated using an extrusion granulator, and then formed into core granules for producing granules.

[0005]

The uncoated or core granules obtained in this manner can be formed into an enteric preparation by coating the core granules with enteric coating. However, in order to eliminate detrimental effects due to the enteric coating base, 1-2 layers of undercoating is applied to the uncoated or core granule. Examples of undercoating bases that can be cited include hydroxypropylmethylcellulose, hydroxypropylcellulose and polyvinylpyrrolidone. Substances that can be added to the undercoating layer include

acid controlling substances having buffering action such as magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium silicate, synthetic hydrotalcite, aluminum hydroxide, aluminum glycinate, aluminum hydroxide-sodium bicarbonate coprecipitate, and as necessary, the aforementioned buffering agents. In addition, examples of enteric coating agents that can be used include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, polyvinyl acetate phthalate, carboxymethylethylcellulose and methacrylic acid-acrylic acid copolymer (product name Eudragit). The enteric tablet or granule that is of a dosage form that is appropriate for oral administration can be obtained as described above, and in addition, the granules can be packaged into capsules to produce a capsule. The preparation obtained in this manner experiences little change in external appearance even over long-term storage, and exhibits excellent stability with almost no decrease in content. The preparation of the present invention also has excellent stomach acid secretion inhibition action and antiulcer action, along with low toxicity. As a result, the preparations can be used in the treatment of digestive ulcers in mammals including humans.

[0006]

[Working examples] The present invention is described in additional detail below by providing working examples and application examples, but the present invention is not restricted to these examples.

#### Working Example 1

100 mg of omeprazole, 100 mg of various amino acids and 100 mg of disodium hydrogen phosphate ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ) used as buffering agent were dispersed in 20 mL of water. While maintaining a temperature of 25°C, the change in external appearance over time of the white dispersion was investigated. In addition, the change in external appearance over time at 25°C was observed for a control solution that did not contain either the amino acid or the buffering agent.

[0007]

Table I

		Additive (mg)		Change in appearance, 25°C			
				1 day	3 days	7 days	
Present	Invention	Glycine	100	White	White	White	
		Na <sub>2</sub> HPO <sub>4</sub> ·12H <sub>2</sub> O	100				
		L-Alanine	100	White	White	Gray-white	
		Na <sub>2</sub> HPO <sub>4</sub> ·12H <sub>2</sub> O	100				
		L-Threonine	100	White	White	Gray-white	
		Na <sub>2</sub> HPO <sub>4</sub> ·12H <sub>2</sub> O	100				
		L-Isoleucine	100	White	White	White	
		Na <sub>2</sub> HPO <sub>4</sub> ·12H <sub>2</sub> O	100				
		L-Phenylalanine	100	White	White	Gray-white	
		Na <sub>2</sub> HPO <sub>4</sub> ·12H <sub>2</sub> O	100				
		None	--	Light purple	Purple	Black-purple	
		Amino acid	Glycine	100	Purple	Purple	Black-purple
			L-Alanine	100	Light purple	Purple	Black-purple
			L-Isoleucine	100	Light purple	Purple	Black-purple
			Buffering Agent	Na <sub>2</sub> HPO <sub>4</sub> ·12H <sub>2</sub> O	100	Light brown	Light brown
		Sodium polyphosphate		200	Brown tint	Brown tint	Light brown
Sodium pyrophosphate	200	Brown tint		Brown tint	Light brown		
Sodium tartrate	200	Light purple		Purple	Purple		
Sodium acetate	200	Brown tint		Light purple	Light purple		
Sodium bicarbonate	200	White		Brown tint	Light purple		
Disodium hydrogen phosphate	200	Light brown		Light brown	Light brown		
Magnesium carbonate	200	White		Brown tint	Light brown		

[0008]

As a result, it was clear that the use of amino acid and buffering agent in conjunction inhibited omeprazole discoloration better than when either substance was used individually, and that the use of these substances in conjunction stabilized the omeprazole.

[0009]

#### Working Example 1

In the composition indicated below, the omeprazole, crystalline cellulose, hydroxypropylcellulose with a low degree of substitution, hydroxypropylcellulose and mannitol were introduced into a kneader, and were mixed for about 20 min. A solution produced by dissolving glycine and sodium dihydrogen phosphate (Na<sub>2</sub>HPO<sub>4</sub>·12H<sub>2</sub>O) in an appropriate amount of water was then added to this material, and kneading was

performed. The material was then dried for 30 min at 50°C in a fluidization dryer. After drying, a screen was used to obtain 14-24 mesh granules.

Omeprazole	5.0 mg
Glycine	2.5 mg
$\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$	2.5 mg
Crystalline cellulose	4.0 mg
Low-substitution hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	56.5 mg
Total	75.0 mg

[0010] Working Example 2

Granules were obtained from the following composition according to Working Example 1. The L-glutamic acid sodium salt and sodium pyrophosphate were dissolved in purified water and blended.

Omeprazole	5.0 mg
L-glutamic acid sodium salt	2.5 mg
Sodium polyphosphate	1.0 mg
Crystalline cellulose	4.0 mg
Low-substitution hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	58.0 mg
total	75.0 mg

[0011].Working Example 3

Granules were obtained from the following composition according to Working Example 1. The L-alanine and dipotassium hydrogen phosphate ( $K_2HPO_4$ ) were dissolved in purified water and blended.

Omeprazole	5.0 mg
L-Alanine	1.5 mg
$K_2HPO_4$	1.5 mg
Crystalline cellulose	4.0 mg
Low-substitution hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	58.5 mg
total	75.0 mg

[0012] Working Example 4

A coating of the following composition was applied to the granules obtained in Working Example 3 to obtain enteric granules. The undercoatings 1 and 2 were applied using a fluidization spray dryer (Okawara) at a feed gas temperature of 75°C and an exhaust gas temperature of 55°C. The enteric coating was applied at a feed gas temperature of 65°C and an exhaust gas temperature of 50°C.

Granules of Working Example 3	75.0 mg
Undercoating 1	
Hydroxypropylmethylcellulose	3.5 mg
Synthetic hydrotalcite	1.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)

Total	5.5 mg
Undercoating 2	
Hydroxypropylmethylcellulose	3.5 mg
Titanium oxide	2.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	6.5 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	10.7 mg
Cetanol	0.5 mg
Talc	1.8 mg
Methylene chloride	(33.0 mg)
Ethanol	(86.0 mg)
Purified water	(33.0 mg)
Sum	13.0 mg
Total	100.0 mg

[0013] Working Example 5

In the following composition, the omeprazole, mannitol, Explotab, sodium laurylsulfate and hydroxypropylcellulose were mixed until uniform, and a solution of L-isoleucine and sodium pyrophosphate dissolved in an appropriate amount of purified water was added thereto. After mixing, the material was dried in a fluidization dryer at 50°C for 30 min. The dried granule powder was then sized with a 24 mesh screen, and magnesium stearate was added. Subsequently, 135 mg tablets (uncoated tablets) were manufactured with a rotary tabletizer.



Omeprazole . . . .	20.0 mg
L-isoleucine	3.0 mg
Sodium pyrophosphate	3.0 mg
Mannitol	99.2 mg
Explotab (generic name: carboxymethylstarch sodium)	8.0 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

[0014] Working Example 6

A coating of the following composition was applied to the tablets (uncoated tablets) obtained in Working Example 5 to obtain enteric tablets. The undercoatings 1 and 2 were applied using a Hicoater (Freund Co., Ltd.) at a pan rotation rate of 13 rpm, a feed gas temperature of 70°C and an exhaust gas temperature of 40°C. The enteric coating was applied at a feed gas temperature of 55°C and an exhaust gas temperature of 37°C.

Tablet of Working Example 5	135 mg
-----------------------------	--------

Undercoating 1

Hydroxypropylmethylcellulose	1.5 mg
Cumulite (generic name: aluminum hydroxide-sodium bicarbonate coprecipitate)	0.4 mg
Purified water	(23.0 mg)
Total	1.9 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.1 mg
Titanium oxide	1.0 mg
Purified water	(56.0 mg)
Total	4.1 mg

#### Enteric coating

Hydroxypropylmethylcellulose phthalate	3.1 mg
Cetanol	0.2 mg
Talc	0.2 mg
Ethanol	(35.0 mg)
Purified water	(10.0 mg)
Sum	3.5 mg
Total	144.5 mg

[0015]

#### Working Example 7

Core granules having the formulation presented below were manufactured according to Working Example 1. The glycine and sodium pyrophosphate that were used as stabilizers were dissolved in purified water and blended. Cumulite and disodium hydrogen phosphate ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ) were blended in the undercoating (1) with the objective of preventing blending and modification between the omeprazole in the core grains and the enteric coating. A fluidization spray dryer (Okawara) was used for the film coating. Undercoatings 1 and 2 were applied at a feed gas temperature of 75°C and a exhaust gas temperature of 55°C. The enteric coating was applied at a feed gas temperature of 55°C and an exhaust gas temperature of 40°C.

#### Core granules

Omeprazole	5.0 mg
Glycine	2.0 mg
Sodium pyrophosphate	2.0 mg
Crystalline cellulose	4.0 mg
Low-substitution hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	52.5 mg
total	70.0 mg

#### Undercoating 1

Hydroxypropylmethylcellulose	3.2 mg
Cumulite (generic name: aluminum hydroxide- sodium bicarbonate coprecipitate)	1.2 mg
$\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$	0.1 mg
Talc	0.5 mg
Purified water	(60.0 mg)
total	5.0 mg

#### Undercoating 2

Hydroxypropylmethylcellulose	3.5 mg
Titanium oxide	1.0 mg
Talc	0.5 mg

Purified water	(65.0 mg)
Total	5.0 mg

#### Enteric coating

Eudragit L-30D-55 (solid)	15.0 mg
(genetic name: methacrylic acid acrylic acid copolymer)	
Polyethylene glycol 6000	1.3 mg
Tween 80	0.7 mg
Talc	3.0 mg
Purified water	(50.0 mg)
Sum	20.0 mg
Total	100.0 mg

[0016]

#### Effect of the invention

Stabilization effects were not obtained when the amino acid, amino acid acid salt or amino acid alkali salt and the buffering agent were used individually and blended in benzimidazole compound. However, it was found that the benzimidazole compound was extremely stable when these substances were used in conjunction. Preparations containing stabilized antiulcer agent were obtained by using these substances in conjunction.